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REVIEW

Cytokine storm and translating IL-6 biology into effective treatments for COVID-19

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Abstract **As of May 3, 2023, the coronavirus disease 2019 (COVID-19) pandemic has resulted in more than 760 million confirmed cases and over 6.9 million deaths. Several patients have developed pneumonia, which can deteriorate into acute respiratory distress syndrome. The primary etiology may be attributed to cytokine storm, which is triggered by the excessive release of proinflammatory cytokines and subsequently leads to immune dysregulation. Considering that high levels of interleukin-6 (IL-6) have been detected in several highly pathogenic coronavirus-infected diseases, such as severe acute respiratory syndrome in 2002, the Middle East respiratory syndrome in 2012, and COVID-19, the IL-6 pathway has emerged as a key in the pathogenesis of this hyperinflammatory state. Thus, we review the history of cytokine storm and the process of targeting IL-6 signaling to elucidate the pivotal role played by tocilizumab in combating COVID-19.**

Keywords SARS-CoV-2; COVID-19; cytokine storm; interleukin-6; tocilizumab

Introduction

At the end of 2019, severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) initiated a global epidemic of a human-to-human pandemic disease, which was named as coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) [1]. Unprecedented difficulties have been posed to the global healthcare system by this pandemic. Up to May 3, 2023, there were 765 222 932 confirmed cases of COVID-19 worldwide with a reported death toll of 6 921 614 as on statistics made public by the WHO [2]. The median incubation after SARS-CoV-2 infection is 4 days [3]. Over 80% of individuals have mild disease, and clinical symptoms might vary in severity [4,5]. Considering that SARS-CoV-2 primarily targets the upper respiratory tract, most patients report symptoms like sore throat, dry cough, and fever [3,6–8]. Invading the lower respiratory tract can cause acute lung damage and can induce acute respiratory distress syndrome (ARDS) within a median period of 8 days from disease onset [8]. These conditions are detected in chest computed tomographic images as bilateral patchy shadows or ground glass opacity [9–11]. SARS-CoV-2 gains entry into host cells through the angiotensin-converting enzyme 2 receptor, which confers the virus with the potential to invade various organs and systems. Zou *et al.* constructed a risk map indicating the potential risk of different organs to SARS-CoV-2 infection [12]. The reported symptoms and complications encompass olfactory and gustatory dysfunctions, anorexia, nausea or vomiting, diarrhea, heart palpitations, myocardial injury, heart failure, liver dysfunction, kidney injury, thrombosis, myalgia or arthralgia, headache, fatigue, stroke, mental disorders, conjunctival congestion, and ocular pain [3,6,8,13–30]. The conditions may progress rapidly to varying degrees of dyspnea, septic shock, disseminated intravascular coagulation (DIC), uncorrectable metabolic acidosis, and multi-organ failure requiring admission to an intensive care unit (ICU) [31]. These conditions are associated with poor prognosis and high mortality rates.

Patients admitted to an ICU exhibit an increased level of interleukin (IL) 2, IL-7, IL-10, interferon-γ-inducible

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protein 10 (IP10), granulocyte-colony-stimulating factor (G-CSF), tumor necrosis factor α (TNF-α), monocyte chemoattractant protein 1 (MCP1), and macrophage inflammatory protein 1 alpha (MIP1A) compared with non-ICU patients [7]. In addition, Yang *et al.* found that IL-1α, IL-6, macrophage-colony-stimulating factor (M-CSF), IP10, MCP-3, MIP1α, hepatocyte growth factor, and monokine-induced gamma IFN were highly expressed in patients with critical and severe COVID-19 [32]. Lymphocytopenia was observed in most patients, and this condition exhibited a considerable correlation with disease severity [3,6–8,13,33–35]. An autopsy report from COVID-19 that progressed to ARDS revealed the presence of lymphocyte-dominant interstitial mononuclear inflammatory infiltrates in both lungs [36]. Zhou *et al.* performed immune analysis on peripheral blood samples obtained from patients with severe COVID-19 and identified heightened levels of granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-6 [33]. These investigations have revealed that patients with COVID-19 experience a cytokine storm, indicating that blocking the inflammatory storm could serve as an efficacious treatment for severe COVID-19.

By competitively inhibiting the binding of IL-6 to its receptors, tocilizumab effectively blocks the signal transduction pathways mediated by IL-6. The US Food and Drug Administration (FDA) has approved the treatment of rheumatologic conditions [37–39] and cytokine storm associated with chimeric antigen receptor T cell therapy [40–42]. Considering the benefits of clinical trials, tocilizumab was granted emergency approval by the FDA on June 24, 2021, for the treatment of COVID-19 in hospitalized adults and pediatric patients (2 years old and above) who were receiving systemic corticosteroid therapy and requiring oxygen therapy, mechanical ventilation, or extracorporeal membrane oxygenation [43]. The WHO also strongly recommended the use of tocilizumab in patients with severe or critical COVID-19 on July 6, 2021 [44]. This review aims to investigate the role of cytokines in COVID-19 pathogenesis, providing comprehensive understanding of viral-induced inflammatory storm and exploring the efficacy and global application of tocilizumab as a treatment.

Cytokine storm

Cytokine storm pathology

Cytokines are a complex group of small proteins that are secreted by cells for signal transduction, including IL, chemokines, TNF, CSF, and interferon (IFN). They play a pivotal role in regulating immune and inflammatory responses [45–47]. The immune system, comprising innate and adaptive immunity, induces and activates the release of cytokines to eliminate pathogens and restore immune homeostasis in response to foreign invaders. However, the excessive activation of cytokines disrupts the balance between anti-inflammatory and pro-inflammatory responses, causing hyperinflammation responses and multi-organ failure, which is known as cytokine storm [46,48]. This concept was first proposed in 1993 by Ferrara *et al*. [49] and then appeared more frequently in scientific research. Cytokine storm can be induced by a diverse range of infectious and non-infectious etiologies, encompassing various therapeutic interventions, pathogens, cancers, autoimmune disorders, and monogenic disorders [48].

In sensing invading viruses, the innate immune system serves as the first line of defense by recognizing and responding to pathogen-associated molecular pattern molecules through cytoplasmic pattern recognition receptors, thereby initiating the expression of IFN, the activation of antiviral cells, and the release of pro-inflammatory cytokines [50,51]. These processes subsequently trigger the activation of the adaptive immune system for combating infections [52]. The immune cells serve as vigilant guardians of the body safeguarding it against damaged cells and infectious agents, while mediating the inflammatory response by inducing the secretion of cytokines and chemokines. Excessive inflammatory innate responses in conjunction with impaired adaptive immune responses can result in tissue damage [53]. The innate immune cells predominantly involved in cytokine storm include neutrophils, macrophages, mast cells, and natural killer (NK) cells [54]. Neutrophils play a pivotal role in thrombosis and enhance cytokine production during cytokine storm [55]. Macrophages can induce severe tissue and organ damage by secreting excessive amounts of cytokines, and their activation by IFN-γ results in the consumptive anemia of inflammation [56]. Mast cells may release histamine to increase the production of IL-1 [57]. In addition, SARS-CoV-2 triggers the activation of alveolar macrophages through Toll-like receptors (TLRs), leading to IL-1 production, which in turn stimulates mast cells to secrete IL-6. As a prominent pro-inflammatory cytokine in cytokine storm, IL-1 plays a vital role in acute inflammatory responses by recruiting immune cells and inducing secondary cytokine production [58]. Elevated levels of IL-1 may be associated with the pathogenesis of systemic inflammation, coagulation disorders, and thrombotic complications [59,60]. SARS-CoV-2 can activate mast cells through TLRs, thereby inducing the release of proinflammatory mediators and triggering a cytokine storm that disrupts the blood–brain barrier and facilitates viral entry into the brain [61]. Increased inflammatory mediators may cause the activation of glial cells and neuron, and cause stroke, neuroinflammation, neurodegeneration, cognitive dysfunction, and neuronal

death. In addition, an article has suggested that an inflammatory immunoreactivity occurs in glioma and glioblastoma [62]. NK cells can kill infected cells and secrete regulatory cytokines; however, their cytolytic function is ineffective in some forms of cytokine storm [63]. Excessive levels of IL-6 may inhibit the function of NK cells, resulting in prolonged antigen stimulation and hindering the resolution of inflammation [64]. T cell-mediated adaptive immune responses play a pivotal role in viral clearance and long-term antiviral immunity; however, they may contribute to the development of cytokine storm. Type 1 helper T (Th1) cells, Th2 cells, Th9 cells, and Th17 cells can recruit macrophages, eosinophil, basophils, mast cells, and neutrophils to initiate inflammatory responses [65–67]. In addition, cytotoxic T lymphocytes are essential for the control of viral infections. After SARS-CoV-2 infection, the increased release of IL-6 and IL-10 was shown to upregulate the expression level of NKG2A on CD8 T cells, which curbs the expansion of CD8 T cells and leads to the functional exhaustion of cytotoxic lymphocytes associated with disease progression [68,69].

Through systemic circulation, the inflammation induced by cytokine storm travels broadly throughout the body from its localized origin [46]. Fever is a common manifestation observed in most patients. In addition, patients may experience respiratory symptoms (e.g., cough, sputum, dyspnoea), fatigue, gastrointestinal reactions, headache, rash, arthralgia, myalgia, and neuropsychiatric symptoms [70,71]. The repair process begins shortly after the onset of inflammation, and repair may culminate in complete restoration of tissue and organ function. Conversely, persistent organ dysfunction may result from serious inflammation or damage to the local tissue structure caused by inflammation. Patients may present with ARDS, multiple-organ failure, DIC, shock, and death. According to Fajgenbaum *et al.*, cytokine storm may occur based on the following three criteria: elevated levels of circulating cytokines, acute systemic inflammatory symptoms, and either secondary organ dysfunction resulting from inflammation beyond that which could be attributed to a normal response to a pathogen (if present) or any cytokine-driven organ dysfunction (if no pathogen is present) [48].

Highly pathogenic coronaviruses may trigger cytokine storm [7,72,73]. Rapid viral replication and excessive proinflammatory cytokine/chemokine production may lead to the apoptosis of respiratory epithelial and endothelial cells [74,75]. The mechanism underlying this apoptosis involves the Fas/FasL or tumor necrosis factor-related apoptosis-inducing ligand/death receptor 5 pathway caused by IFN-αβ and IFN-γ-induced inflammatory cell infiltration [76–81]. Inflammation then leads to extensive pulmonary congestion and edema as well as the formation of hyaline membrane in the alveolar cavity, causing intractable hypoxemia and respiratory distress, which was known as ARDS [82,83]. Histopathological findings of the lungs revealed diffuse alveolar damage and infiltration of interstitial or intra-alveolar inflammatory cells in patients diagnosed with 2009 influenza A (H1N1) [84]. Similar pathological features can also be observed in SARS, MERS, and COVID-19 [36,85,86]. In addition, excess cytokines can diffuse into the circulatory system and cause systemic inflammatory response syndrome. The collateral damage of the immune response caused by cytokines may pose a more lethal threat than the pathogen itself. Therefore, identifying and blocking the cytokine pathways that cause the inflammatory storm are critical to reducing the rates of serious illness and mortality.

Cytokine storm in highly pathogenic coronaviruses

Coronaviruses are a group of highly infectious and pathogenic viruses that have attracted global attention. They belong to the category of enveloped, positive-sense, single-stranded RNA viruses, which are classified into two varieties: low-pathogenicity and high-pathogenicity coronaviruses [87,88]. The former infects the upper respiratory tract and causes mild symptoms, whereas highly pathogenic coronaviruses such as SARS-CoV [89], the Middle East respiratory syndrome coronavirus (MERS-CoV) [90], and SARS-CoV-2 [1] likely invade the lower respiratory tract, leading to the development of severe pneumonia associated with cytokine storm [87,91].

In 2002, the emergence of SARS, a highly contagious illness caused by SARS-CoV and first appeared in China, had significant global implications [92]. The autopsy report revealed diffuse alveolar damage [93,94]. The presence of hemophagocytic syndromes supported the hypothesis of cytokine dysregulation [94]. IL-6, IL-8, and TNF-α were among the initial cytokines that exhibit rapid elevation in the blood during early stages of infection [95]. The induction of IP10 and IL-2, as well as the consequent overproduction of IL-6 and the lack of IL-10 production, was a critical event in initiating immune-mediated acute lung injury and lymphocyte apoptosis [96]. In addition, chemokines, such as CCL2, CCL3, CCL5, CCL10, and CXCL10, were significantly upregulated at 24 h [97–99]. High levels of cytokines (IL-1, IL-6, IL-12, IL-18, IFN-γ, and TGFβ) and chemokines (IL-8, CCL2, CXCL9, and CXCL10) were detected in patients severely infected with SARS compared with those with uncomplicated cases [96,100,101]. The pathogenesis of SARS could be attributed to dysregulation in the production of IFN-α and IFN-γ, as well as the transcription of IFN-stimulated genes [100,102,103].

MERS, caused by MERS-CoV, primarily occurred in Saudi Arabia and became endemic in 2012 [104]. Similar

to SARS, autopsy results revealed that diffuse alveolar damage was the most characteristic manifestation of MERS lungs [86]. An *in vitro* study revealed that MERS-CoV infection induced higher levels of IL-8, IL-12, IFN-γ, CCL2, CCL3, CCL5, and CXCL10 compared with SARS-CoV, whereas TNF-α and IL-6 levels were comparable between the two viruses [73]. The cytokine profiles of MERS in plasma samples were analyzed using cytometric bead array, showing a significant upregulation in IFN-α2, IFN-γ, IL-10, TNF-α, IL-15, and IL-17 compared with the healthy controls [105]. Elevated levels of IL-6 and CXCL10 were detected in patients infected with MERS-CoV, which may be associated with the severity of pneumonia [106]. Upon infecting the human airway epithelial cells, analysis of mRNA expression of eight cytokines revealed that MERS-CoV induced a delayed yet significant induction of IL-1β, IL-6, and IL-8 compared with SARS-CoV [107].

COVID-19, caused by another β-coronavirus known as SARS-CoV-2, was declared a pandemic in March 2020 [108]. Bilateral diffuse alveolar damage with infiltration of mononuclear inflammatory lymphocytes was observed in biopsy samples obtained postmortem from a patient who succumbed to severe COVID-19 [36], indicating the occurrence of cytokine storm. A previous study of 41 cases in Wuhan found that patients infected with SARS-CoV-2 exhibited higher levels of IL-1B, IL-1RA, IL-7, IL-8, IL-9, IL-10, IP10, TNF-α, IFN-γ, basic FGF, G-CSF, GM-CSF, MCP1, MIP1A, MIP1B, PDGF, and VEGF concentrations in their plasma compared with non-infected individuals. Meanwhile, in patients admitted to an ICU as opposed to non-ICU ones, the levels of IL-2, IL-7, IL-10, TNF-α, G-CSF, MCP1, MIP1A, and IP10 were high [7]. Xiong *et al*. observed significantly elevated expression levels of CXCL1, CXCL2, CXCL6, CXCL8, CXCL10, CCL2, CCL3, and CCL4 in the bronchoalveolar lavage fluid of patients with COVID-19 compared with the control group [109]. Furthermore, high levels of CCL2, CXCL2, CXCL8, and CXCL10 can facilitate the recruitment of immune cells to the infection site, potentially leading to exacerbating lung inflammation [109–111]. IL-6, IL-17, TNF-α, TGF-β, IFN, and CXCL10 may contribute to lung injury following SARS-CoV-2 infection [112]. Analysis of the immunopathology of SARS-CoV-2 conducted by Zhou *et al.* indicated that excessive activation of the immune response was likely responsible for acute pulmonary injury following SARS-CoV-2 infections [33].

Elevated levels of IL-6 in COVID-19

IL-6 is a pleiotropic cytokine secreted by various cell types. As a pyrogen, the diverse functions of IL-6 include increasing antibody production and inducing the expression of acute-phase reactants [48]. SARS-CoV-2 infection of diverse immune cells, including monocytes, macrophages, dendritic cells, and T cells, results in their activation and secretion of IL-6 (Fig. 1) [33,113–118]. The activation of the NF-κB pathway mediated by TLRs, as well as IL-1, IL-18, and TNF, is a strong stimulator of IL-6 synthesis [119–122]. However, excess IL-6 may also suppress IL-1 on the level of transcription [123].

IL-6 has two primary signal transduction pathways (Fig. 1). Classic *cis*-signaling via the membrane-bound IL-6 receptor (mIL-6R) is primarily anti-inflammatory, whereas *trans*-signaling via soluble IL-6R (sIL-6R) is rather pro-inflammatory [124]. This complex subsequently binds to gp130 on the cell membrane and then activates downstream signal transduction pathways, including the JAK-STAT3 pathway and JAK-SH2 domain tyrosine phosphatase 2 (SHP2)-mitogen-activated protein kinase pathway [125–128]. Then, a cascade of signaling events is started, promoting the transcription of multiple downstream genes and controlling the production of proteins implicated in the regulation of gene expression. As a warning signal during viral infection, IL-6 was thought to be related to antiviral activity, promoting inflammation resolution and tissue remodeling [129–131]. However, a study has indicated that high levels of IL-6 following viral infection promoted the generation of pathogenic Th17 cells capable of producing IL-17. The synergistic effect of IL-6 and IL-17 may impact the host's immune defense mechanism, leading to a persistent state of viral infection [132]. Elevated levels of IL-6 were detected in patients and mouse models who developed cytokine release syndrome following CAR T cell therapy [133–135], highlighting the pivotal role of this cytokine in the pathogenesis of cytokine storm.

A number of studies have found that patients with COVID-19, particularly those with serious conditions, have high expression of IL-6 [6,7,33,35,136–138]. Meta-analysis of six studies has found that patients with complicated COVID-19 (defined as ARDS, requiring ICU admission, or classified as severe or critical cases) had IL-6 levels 2.90-fold higher than those with non-complicated disease [138]. The findings of another meta-analysis have demonstrated a correlation among elevated IL-6 levels, disease progression, and an increased risk of mortality [139]. They also proposed employing a cut-off value of more than 55 and 80 pg/mL for IL-6 to identify patients at high risk of severe disease and mortality, respectively [139]. These reports have provided evidence for the significance of IL-6 as a biomarker for assessing disease severity and predicting death, as well as its involvement in COVID-19 pathogenicity. However, Yin *et al.* have demonstrated that increased levels of IL-6 may also serve as a predictive marker for long COVID-19,

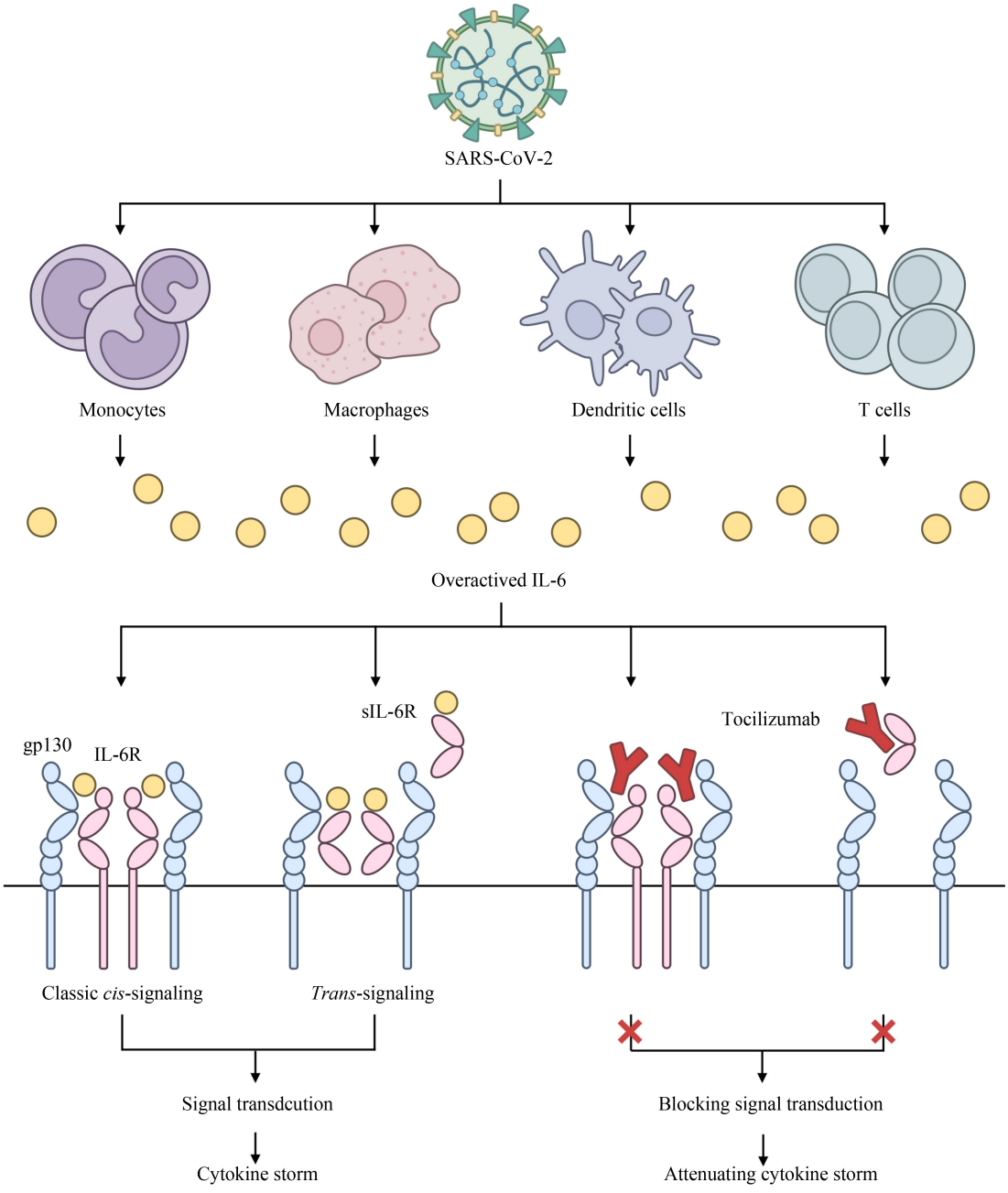

Fig. 1 Cell signaling pathways of overactivated IL-6 in COVID-19. SARS-CoV-2 infection induces the activation of diverse immune cells, including monocytes, macrophages, dendritic cells, and T cells, leading to the secretion of interleukin-6 (IL-6). IL-6 receptor (IL-6R) has two forms: membrane-bound interleukin-6 receptor (mIL-6R) and soluble interleukin-6 receptor (sIL-6R). The formation of a complex between IL-6 and mIL-6R or sIL-6R is followed by its subsequent binding to gp130 on the cell membrane. The overproduction of IL-6 initiates a cascade of signaling transduction through classic *cis*- and *trans*-signaling pathways, thereby inciting a cytokine storm and contributing to an immune disorder in severe COVID-19. As a recombinant humanized monoclonal antibody, tocilizumab can specifically target mIL-6R and sIL-6R, thereby interfering with *cis*- and *trans*-signaling pathways to block signal transduction and attenuate cytokine storm.

with an average value of 20.92 pg/mL (compared with the mean value of 5.186 pg/mL in healthy individuals) [140]. The dysregulation of the immune response to COVID-19 has been reported to contribute to the involvement of IL-6. On the one hand, IL-6 may interfere with antiviral defenses by inducing dysfunction in NK cells and inhibiting perforin and granzyme B [64,141]. On the other hand, the IL-6-mediated downregulation of HLA-DR expression on CD14 monocytes and lymphopenia was associated with sustained cytokine production and excessive inflammatory response [142]. IL-6 promotes the differentiation of T cells into Th17 cells and

subsequently inhibits the differentiation of regulatory T cells (T-reg), thereby disrupting the balance in T-reg/Th17 and contributing to the pathogenesis of ARDS [143]. Therefore, targeting IL-6 could serve as a promising therapy to prevent disease progression and mitigate mortality.

Tocilizumab for the treatment of COVID-19

Tocilizumab is a highly efficacious monoclonal antibody against IL-6R with remarkable specificity for sIL-6R and mIL-6R, thereby interfering with *cis*- and *trans*-signaling pathways to inhibit signal transduction (Fig. 1). Tocilizumab, which is initially approved as an orphan drug in Japan for the treatment of Castleman's disease in 2005 [144], has been licensed in the FDA for treating adult patients who have moderate-to-severe active rheumatoid arthritis and have had an inadequate response to disease-modifying anti-rheumatic drugs [145,146], giant cell arteritis [147,148], active polyarticular juvenile idiopathic arthritis [149], active systemic juvenile idiopathic arthritis [150,151], scleroderma-associated interstitial lung disease [152], and CAR T cell-induced severe or life-threatening cytokine release syndrome [40,42].

Based on the observed efficacy of tocilizumab in managing severe cytokine storm induced by CAR T cell therapy with elevated IL-6 levels, as well as analysis of the immune profile in patients with severe COVID-19 [33], we initiated a clinical investigation and registered a multicenter clinical trial (ChiCTR2000029765) in February 2020 to evaluate the effectiveness of tocilizumab in the treatment of patients with severe or critical COVID-19 [153,154]. In the initial uncontrolled trial, a total of 21 patients received tocilizumab at an initial dose ranging from 4 to 8 mg/kg body weight, with a recommended dosage of 400 mg administered intravenously up to a maximum of 800 mg. If fever occurred within a 12 h period, then an additional dose (same as before) should be administered. The cumulative dosage could not exceed two times the recommended amount. The findings of this study have indicated that tocilizumab could serve as a potential therapeutic intervention for COVID-19 because of its application potential in reducing cytokine storm and improving clinical symptoms such as body temperature, hypoxemia, and CT opacity changes. Following the publication of our retrospective report in the Proceedings of the National Academy of Sciences [153], Dr. Anthony L. Komaroff, the founding editor of NEJM Journal Watch and NEJM Journal Watch General Medicine, commended the impressive findings. Thus, further clinical trials are necessary to identify subsets of patients who are most likely to benefit from the drug [155]. On March 3, 2020, treatment with tocilizumab as a method of immunotherapy was incorporated into the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia in China (7th Interim Edition) [156]. After 1 month, tocilizumab was recommended by the Infectious Diseases Society of America for clinical trials [157]. Similarly, the National Institutes of Health (NIH) moderately recommended tocilizumab for clinical trials in guidelines update on August 27, 2020 [158]. The progression of tocilizumab from basic research to clinical application is shown in Fig. 2. Subsequently, tocilizumab has been registered for clinical trials worldwide to evaluate its efficacy in SARS-CoV-2-induced inflammatory storm. Our administration protocols of tocilizumab, as described above, have served as a reference for almost all tocilizumab regimens in COVID-19, which are intended for short-term use. A search conducted on clinicaltrials.gov identified a total of 75 registered clinical trials evaluating the efficacy and safety of tocilizumab for COVID-19, with 29 having been completed to date.

Previous clinical trials have demonstrated the limited efficacy of tocilizumab in providing significant therapeutic benefits for patients with COVID-19 [159–165]. In a phase 3 trial of patients with severe COVID-19, tocilizumab has demonstrated no significant improvement in their clinical status or reduced mortality at 28 days [162]. Similar outcomes were observed in a randomized clinical trial of 126 hospitalized patients with COVID-19 with a PaO_2/FiO_2 ratio ranging from 200 to 300 mmHg [166]. Clinical deterioration was observed in 28.3% of patients treated with tocilizumab within 14 days, as compared with 27.0% in the standard care group. Another trial has shown a 17% mortality rate at 15 days among patients in the tocilizumab group compared with 3% in the standard care group, indicating that the administration of tocilizumab may increase mortality in severe or critical COVID-19 cases [167]. These findings may be attributed to various factors, including small samples size, patient demographics (such as disease severity, systemic inflammation levels, age, and comorbidities), lack of blinding procedures, and the absence of standardized treatment across trial sites and countries.

However, clinical studies have observed that tocilizumab induced a prompt and sustained response and was associated with a significant clinical improvement [168]. Snow *et al*. have carried out an analytical report to evaluate the therapeutic value of tocilizumab in COVID-19 [169]. The findings indicated that tocilizumab was associated with a decreased requirement for mechanical ventilation (8.7% vs. 10.5%, $P = 0.004$) on conventional analysis alone and a reduced progression-to-severe disease (28.9% vs. 36.6%, $P = 0.002$) compared with standard care. Another meta-analysis, comprising 52 studies with 27 004 patients, has found that tocilizumab exhibited an important survival benefit (11% in

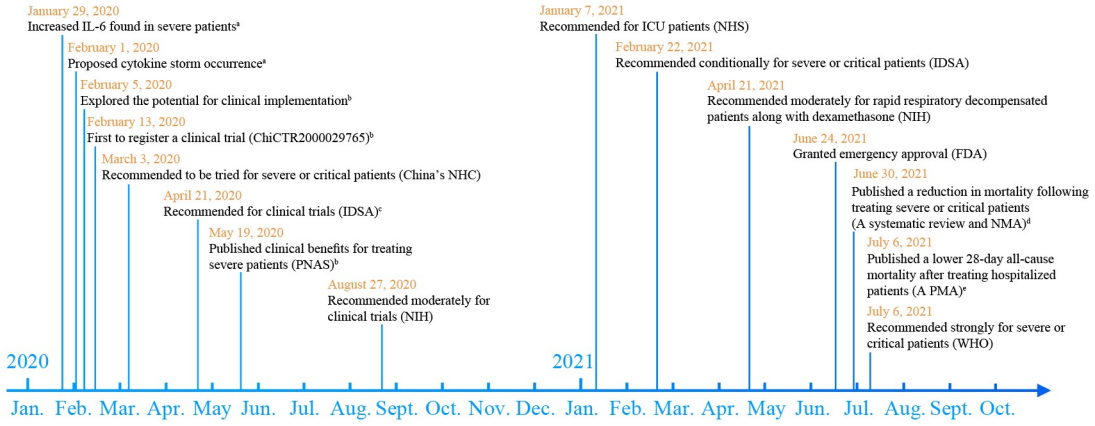

Fig. 2 Timeline of tocilizumab from basic research discovery to clinical application in COVID-19. [a]This article was published in the National Science Review [33]. [b]Xu *et al*. initiated a clinical exploration and reported the benefits in PNAS [153], while registering a multicenter clinical trial (ChiCTR2000029765) to evaluate the efficacy of tocilizumab for patients with severe COVID-19. [c]According to Xu's report, tocilizumab was recommended by IDSA within the context of a clinical trial [157], with 75 registered trials available on clinicaltrials.gov to date. [d]This article was initially preprinted in medRxiv on June 30, 2021 and subsequently published in BMJ Medicine [178]. [e]This article was published online in JAMA on July 6, 2021 [183]. IL-6, interleukin-6; NHC, National Health Commission; IDSA, Infectious Diseases Society of America; PNAS, Proceedings of the National Academy of Sciences; NIH, National Institutes of Health; NHS, National Health Service; FDA, Food and Drug Administration; NMA, network meta-analysis; PMA, prospective meta-analysis; WHO, World Health Organization; JAMA, Journal of the American Medical Association.

randomized controlled trials (RCTs); 31% in observational studies) [170]. Moreover, the requirement for invasive mechanical ventilation was reduced by 19% in RCTs. Based on the RECOVERY trial [171], tocilizumab was related to a higher likelihood of hospital discharge within 28 days and a significant reduction in 28-day mortality compared with the usual care groups. Among patients who were not receiving invasive mechanical ventilation at randomization, tocilizumab decreased the probability of progression to the composite outcome of invasive mechanical ventilation or death. The median duration of hospitalization following early administration of tocilizumab was 9 days, which represented a significant reduction compared with the control group where the median length of stay was 12 days [172]. The improvements have been observed in the levels of ferritin, C-reactive protein, and D-dimer, as well as PaO_2/FiO_2 ratios after tocilizumab administration [168,172–176]. Furthermore, Wang *et al*. have found that treatment with tocilizumab in patients presenting bilateral pulmonary lesions and elevated IL-6 levels was associated with a prompt improvement of hypoxemia and a reduced requirement for increased oxygen inhalation [154]. The use of tocilizumab was identified as an independent predictor of survival in patients with severe COVID-19 and persistent hypoxia based on a retrospective cohort study [177]. The administration of tocilizumab within 6 days from admission may increase the probability of survival [173]. The previously mentioned studies have emphasized the critical significance of the early administration of tocilizumab in the course of disease progression. Moreover, network meta-analysis has suggested that the combination of tocilizumab and corticosteroids likely resulted in reduced mortality compared with the use of corticosteroids alone [178]. Therefore, patients may derive greater therapeutic benefits.

The potential occurrence of adverse events warrants caution. Several clinical trials have concerned about the safety of tocilizumab in treating COVID-19. The most frequently reported adverse reactions included secondary infection, hepatic function abnormality, and neutropenia [159,165–167,171]. Rossotti *et al*. have observed a significantly higher incidence of severe infections exceeding 10%, which may lead to prolonged hospitalization [179]. Contrary to its repeated administration for the treatment of rheumatoid arthritis, tocilizumab was mostly administered as a single dose over a short period in patients with COVID-19 [180]. Some adverse reactions, such as neutropenia, were believed to be associated with the repeated administration of tocilizumab over a longer follow-up period [179]. The evidence of serious adverse events and the risk of bacterial or fungal infections by the WHO were rated as very low and low, respectively [181].

Based on the results from clinical trials, the National Health Service of the UK issued a recommendation on January 7, 2021, endorsing the use of tocilizumab as a therapeutic intervention for patients with COVID-19 admitted to the ICU [182]. In the fifth version of the WHO living guideline, published on July 6, 2021, a strong recommendation was made for tocilizumab in treating severe or critical COVID-19 patients [44]. This recommendation was primarily supported by network

meta-analysis [178] and a prospective meta-analysis [183]. The findings of these studies have demonstrated that patients treated with IL-6 receptor blockers exhibited a significantly reduced mortality rate. The GRADE assessment rated this outcome as high certainty. According to the Japanese Clinical Practice Guidelines for the Management of Sepsis and Septic Shock guideline, which analyzed data from 15 RCTs involving 8318 patients with moderate or severe COVID-19, tocilizumab demonstrated potential efficacy in reducing the all-cause mortality by 32 ‰ and 16 ‰ among moderate and severe patients, respectively, on day 28. In addition, an increase of 35‰ and 12‰ was observed in clinical improvement of patients with moderate and severe COVID-19, respectively [184]. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) also performed a review of several RCTs to access the efficacy and safety of tocilizumab for moderate or severe COVID-19 [185]. The results found that tocilizumab was related to a decrease in mortality and a reduced requirement for mechanical ventilation. The certainty of evidence regarding these findings was rated as moderate and high, respectively. Therefore, they recommend the use of tocilizumab for treating patients with severe COVID-19. Furthermore, tocilizumab has been widely recommended for global use. The recommendations for the use of tocilizumab from several official guidelines are presented in Table 1.

Table 1 Recommended guidelines and indications for the treatment of coronavirus disease 2019 (COVID-19) with tocilizumab

Organization	Conditions
China's NHC[a] (Updated on January 5, 2023)	Recommendation for severe and critical patients with significantly elevated IL-6 levels
WHO[b] (Updated on January 13, 2023)	Strong recommendation for severe or critical patients in combination with corticosteroids
IDSA[c] (Updated on June 26, 2023)	Conditional recommendation for severe or critical patients who exhibit elevated markers of systemic inflammation (low certainty of evidence)
Australian National Clinical Evidence Taskforce (Updated on May 30, 2023)	Conditional recommendation for patients (including adults, pregnant or breastfeeding women, children, and adolescents) who require supplemental oxygen, particularly in the presence of systemic inflammation
NICE[d] (Updated on August 9, 2023)	Recommendation for adult patients who are having systemic corticosteroids and need supplemental oxygen or MV[e]
NIH[f] (Updated on July 21, 2023)	Moderate recommendation for hospitalized patients who are receiving dexamethasone, have systemic inflammation, experience rapidly increasing oxygen needs, and require HFNC[g] oxygen, NIV[h], MV[e] or ECMO[i] (moderate quality of evidence)
ESCMID[l] (Published online on November 21, 2021)	Recommendation for severe patients (quality of evidence: moderate for mortality, high for MV[e])
J-SSCG 2020 Special Committee[m] (Updated in July 2022)	Weak recommendation for moderate patients who require oxygen/hospitalization (moderate certainty of evidence: GRADE 2B); weak recommendation for severe patients who require MV[e]/intensive care (low certainty of evidence: GRADE 2C)

Tocilizumab has gained widespread global recognition and is recommended in some official guidelines with specific indications for its use. The latest version of these guidelines is presented in the table. [a]NHC, National Health Commission; [b]WHO, World Health Organization; [c]IDSA, Infectious Diseases Society of America; [d]NICE, National Institute for Health and Care Excellence; [e]MV, mechanical ventilation; [f]NIH, National Institutes of Health; [g]HFNC, high-flow nasal cannula; [h]NIV, noninvasive ventilation; [i]ECMO, extracorporeal membrane oxygenation; [l]ESCMID, European Society of Clinical Microbiology and Infectious Diseases; [m]J-SSCG, Japanese Clinical Practice Guidelines for the Management of Sepsis and Septic Shock.

Conclusions

Cytokine storm can lead to the progression of COVID-19 into a highly inflammatory, as well as fatal, pulmonary and systemic disease. Therefore, timely intervention in cytokine over-release and cascade reactions is crucial for delaying disease progression and reducing mortality. Considering the pathogenic function of IL-6 signaling in the severe stage of COVID-19, tocilizumab exhibits potential efficacy for patients experiencing severe symptoms through improving clinical symptoms, decreasing requirement for mechanical ventilation, shortening the average length of hospitalization, and reducing the mortality rate. Tocilizumab has been widely recommended as a therapeutic option for severe COVID-19.

Compliance with ethics guidelines

Conflicts of interest Tiantian Li, Dongsheng Wang, Haiming Wei, and Xiaoling Xu declare that they have no conflicts of interest.

This manuscript is a review article and does not involve a research protocol that requires the approval of relevant institutional review board or ethics committee.

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